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PERSPECTIVES IN CLINICAL NEPHROLOGY

D-lactic acidosis: Turning sugar into acids in the gastrointestinal tract

While an appreciable quantity of organic acids is produced each day by bacterial metabolism in the gastrointestinal (GI) tract [1, 2], there is usually no acid-base consequence from this acid load because the rate of production of these acids does not exceed the capacity of the normal host to metabolize them. Nevertheless, after jejuninoileal bypass surgery or substantial small bowel resection, appreciable quantities of acids such as D-lactic acid may accumulate [3–12]. Hence the stage is set for the development of D-lactic acidosis when there is a combination of altered GI anatomy and a change in bacterial flora (such as the use of antibiotics). A less well recognized clinical association is the aggravation of the clinical picture when more glucose is supplied to these bacteria [13–16].

The extent to which production of organic acids will cause metabolic acidosis also depends on biochemical considerations. Not only must one consider whether the patient has the enzymatic machinery to metabolize each added acid, but one must also appreciate the limitations set by the overall rate of ATP turnover in cells [17] and the competition between fuels to be the substrate oxidized to regenerate the ATP needed to perform biologic work in individual cells [18]. Moreover, there is a quantitative relationship between H^+ removal and ATP regeneration that differs between individual organic acids [19].

This manuscript is divided into two sections: first we shall discuss the normal metabolism and functions of organic acids produced in the GI tract; second, we shall consider the different types of presentation of organic acidosis where GI bacteria might have played a central role, highlighting biochemical aspects so that a more rational design for therapy can be suggested.

Organic acids and the GI tract: Normal physiology

There are two sources of organic acids in the GI tract, diet and endogenous production. Organic acids of dietary origin do not usually pose an acid-base threat because the quantity ingested is not large enough to exceed the capacity of the host to remove them by metabolic means. In addition, the intake of acids occurs together with their potassium (K) salts. For example, the citric acid load ingested each day is small and readily metabolized to neutral end-products so it only yields a net H^+ load transiently. Metabolism of the K^+ salt of citrate yields bicarbonate [20]. Overall, after metabolism of the organic acid and its K salt, bicarbonate ions are produced which minimize a threat from another H^+ load. Accordingly, we shall focus on endogenous production of organic acids which are synthesized from neutral precursors (largely carbohydrates) in the lumen of the GI tract. Before discussing factors that influence their rate of production, we shall review their physiologic functions.

Production of organic acids in the GI tract

Acetic acid (60%), butyric acid (20%), and propionic acid (20%) are produced normally in the GI tract [1]. The majority of these organic acids are produced in the caecum because this is the major site where bacteria flourish together with a source of fuel to ferment. The fuels fermented by colonic bacteria are non-digestible fiber, some dietary mono- or disaccharides, and starches that escaped complete digestion and/or absorption upstream in the small intestine. Organic acids are also produced in more distal colon sites; here the fuel is almost exclusively undigested starches and dietary fiber.

The stoichiometry of colonic anaerobic metabolism is that two molecules of organic acid are produced per molecule of hexose (Fig. 1). In quantitative terms, close to 25 g (150 mmoles) of hexose reach the colon, so the overall organic acid production is in the range of 300 mmoles per day [1, 2]. Anaerobic glycolysis can occur at a very rapid rate; D- and/or L-lactic acid are the products of this rapid bacterial metabolism, depending on the predominant bacterial population. If there is sufficient time, certain bacteria have the capacity to metabolize D- or L-lactic acid further and the final product largely becomes acetic acid (Fig. 1). Since the supply of carbohydrate to the colon is not very large, and that there is slow transit, acetic acid is the major organic acid produced during normal anaerobic fermentation [1].

Function of organic acids in the GI tract

The major function of organic acids in the GI tract is to provide a fuel for oxidative metabolism for mucosal cells of the colon. In fact, locally produced butyric acid is a major fuel consumed by colonic mucosal cells [21, 22]. Should the metabolic work of these mucosal cells (ions pumping for the most part) remain high at a time when their supply of butyric acid is curtailed (such as antibiotic therapy), colonic mucosal damage can result [21, 23], which is a nutritional form of colitis.

One can make a rough deduction concerning the load of butyric acid that could be metabolized by mucosal cells of the colon based on their rate of oxygen consumption. Since the splanchnic area consumes close to 25% oxygen utilized at rest (3 out of 12 mmol/min) and considering that the liver requires about 75% of this oxygen, the entire GI tract probably consumes close to 1 mole of O_2 per day [reviewed in 24]. Moreover, the small intestine is the site where most of the biologically active absorption occurs so the colon may consume about 250 mmoles of O_2 daily. Since the stoichiometry is 5 mmoles of O_2 per mmole butyric acid oxidized, the upper limit on its oxidation would be 50 mmoles per day. In addition, since butyric acid supplies only half of the needed ATP in colonic mucosal cells [21,

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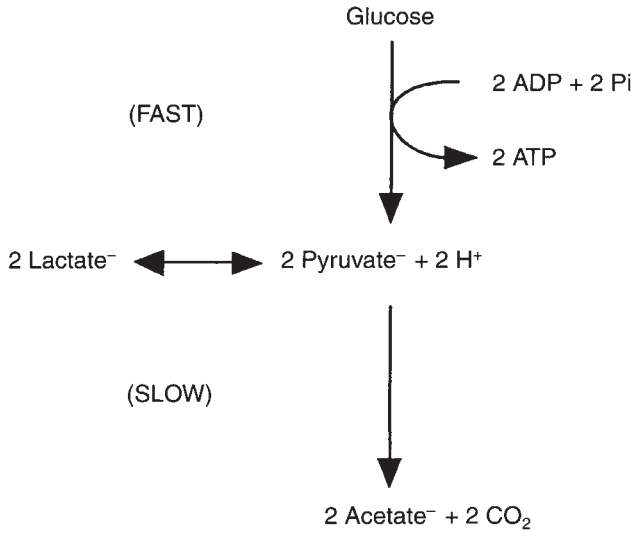

Fig. 1. *Anaerobic fermentation by bacteria in the GI tract.* The product of fermentation reactions depend on the supply of glucose (hexoses), the bacterial population, the local pH, and the time that is available for these reactions to occur. For more discussion, see text. The 2 H^+ accompany pyruvate, lactate and acetate anions.

22], it follows that when more than 25 mmoles of butyric acid are produced, the excess must be metabolized by other organs, excreted as their NH_4^+ salts, or eliminated in the feces as the free acid if acid-base balance is to be maintained.

Absorption of organic acids from the GI tract

There is much less known about the process of absorption of organic acids as compared to the major nutrients in the GI tract. The following general statements reflect the bulk of the data [25–32]. The site of absorption depends on where the organic acids are produced. Although the small intestine has a large capacity to absorb organic acids, few are absorbed here as there is normally little production in the bacteria-poor lumen of the small intestine. Since most organic acids are produced in the colon, most are absorbed there. There are two major proposed mechanisms for organic acid absorption: non-ionic diffusion and the counter-transport of organic anions and bicarbonate ions. A local fall in pH induced by a flux through Na^+/H^+ ion antiporter seems to aid absorption by either mechanism because the secreted H^+ ions favor the formation of the free acid for non-ionic diffusion and the lower concentration of bicarbonate in the lumen will favor its countertransport into, and that of organic acids out of the lumen. The velocity of absorption in some studies is linearly related to the luminal concentration of organic anions and is not saturable, whereas in other experiments, the counter-transport system seems to be dominant and saturable; nevertheless, the capacity for absorption is large. Hence a large amount of organic acids can be absorbed if they are produced rapidly in the GI tract.

Metabolic fates of organic acids added to the body

The metabolic fates of the organic acids produced in the GI tract differ. As discussed above, as much as 50 mmoles of the butyric acid produced can be oxidized directly by the colonic mucosal cells. In contrast, almost all the propionate is cleared by the liver, being converted to glucose, triglycerides or CO_2 [33] (Fig. 2). The acetic acid has two major fates. In the fed state, it is a good substrate for hepatic lipogenesis [34]. In contrast, oxidation is the principal pathway between meals, with most of the acetic acid oxidation taking place in organs other than the liver [24]. With an oxygen consumption rate of 12 mmol/min, the maximum rate of oxidation of acetic acid would be 6 mmol/min because the stoichiometry is 2 mmoles of O_2 per mmole acetic acid oxidized. Obviously this is a gross overestimate because other fuels, such as glucose in the brain [35] and lactate in the kidney [36], are the usual fuels oxidized in normal subjects. The metabolic and biochemical aspects of these processes are addressed later in this paper.

Metabolic acidosis due to over-production of organic acids in the GI tract

Very high rates of production of organic acids in the GI tract will depend on three major factors: (1) the number, location and metabolic capacities of bacteria in the GI tract; (2) the supply of substrates delivered to these bacteria; and (3) the length of time these bacteria and substrates remain in contact in a milieu which is favorable for endogenous acid production (preventing a sudden and large fall in pH in this microenvironment for the most part [5]) (Fig. 3).

Quantitatively, D-lactic acid is normally a minor compound formed in the GI tract. However, if a large quantity of glucose and appropriate bacteria meet in a metabolically friendly environment (a relatively high pH and buffer capacity), anaerobic fermentation by bacteria can be very rapid and L- and/or D-lactic acids will be major products, depending on the specific bacterial population (Fig. 1). When GI bacteria come in contact with a large supply of dietary nutrients, not only are organic acids produced, but also a variety of noxious materials accumulate. These could include aldehydes, alcohols, mercaptans, and amines, some of the latter may act as false neurotransmitters which may explain some of the neurological manifestations commonly seen in these patients [13, 37–39]. It has also been suggested that D-lactate and/or a change in the redox potential might also contribute to these prominent neurological manifestations [40].

Requirements for organic acid over-production in the GI tract

We shall first consider how the system of maintaining separation of sugars and bacteria might break down, and the factors that may favor the over-production of organic acids by bacteria in the GI tract.

Bacteria have not migrated upstream from the colon, but sugar is not absorbed normally in the small intestine. The best example of this scenario is the syndrome of lactose intolerance. In this disorder, the enzyme required to hydrolyze the disaccharide from milk (lactose) does not have sufficient capacity to hydrolyze all the dietary lactose to its component monosaccharides, a required step to permit their complete absorption. Lactose is now delivered to colonic bacteria which metabolize it readily, yielding a variety of organic compounds that cause local irritation to the colonic mucosa. If organic acids are produced and absorbed, this rate of input does not exceed the normal metabolic capacity of the host to remove them so no important systemic acid-base disturbance occurs. One factor that might prevent the development of systemic acidosis is that the acids produced are provided after meals

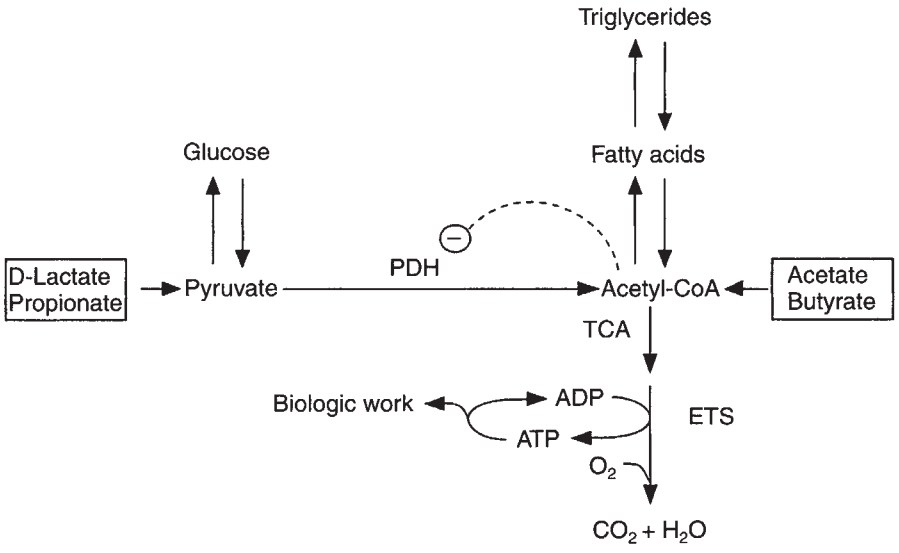

Fig. 2. *Metabolic fate of organic acids produced by the GI tract.* There are two families of organic acids depending on whether they yield pyruvate or not as a metabolic product. Organic anions that cannot be converted to pyruvate can only be oxidized, converted to storage fat, or be converted to ketoacids, and not be substrates for the net synthesis of glucose. Fatty acid synthesis only occurs at appreciable rates when insulin levels are high (with meals). Abbreviations are: PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid cycle; ETS, electron transport system.

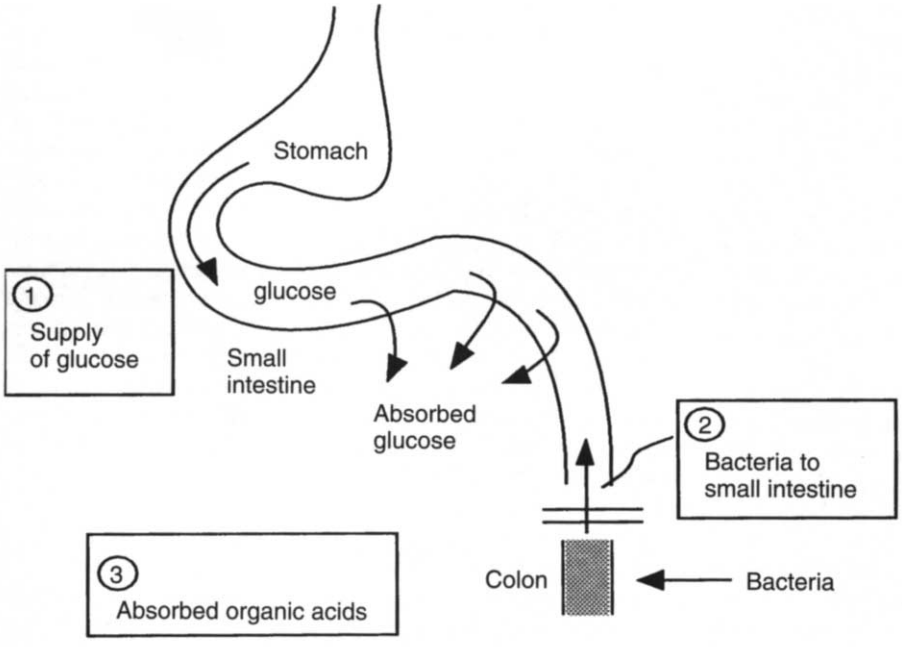

Fig. 3. *Clinical conditions resulting in over-production of organic acids in the GI tract.* For over-production or organic acids by bacterial fermentation, one needs to deliver glucose to bacteria in the colon (poor absorption, rapid transit), or have certain bacteria colonize in the GI tract prior to the site of absorption of glucose. The clinical picture will also depend on whether the acids produced can be absorbed.

when insulin levels are high so that glycogen synthesis [18] and lipogenesis can occur [41] (Fig. 2).

Migration of bacteria up the small intestine so that they can encounter sugars before they are completely absorbed. Bacteria may migrate into, or persist in the lumen of the small intestine for two major reasons. First there may be an anatomical lesion such as a short bowel or a blind loop which provides the opportunity for bacteria to colonize a location prior to complete absorption of sugar. Second, pharmacologic agents or disease states may slow bowel motility to a sufficient degree so that bacteria may migrate into, and multiply in the lumen of the small intestine, thereby accentuating the production and absorption of organic acids (see below).

Conditions favoring over-production of organic acids in the GI tract.

(a) Supply of substrate to the bacteria. There is a clinical observation that in the suitable host, D-lactic acid accumulation may be exacerbated by feeding [13–16]. When there is bacterial overgrowth in the small intestine, the concentration of brush-border enzymes may decrease [27]. Thus ingested disaccharides and complex carbohydrates may not be hydrolyzed at an adequate rate because of low luminal disaccharidase activity. These sugars may then be fermented by bacteria which have colonized the small intestine or may be delivered to the colon where they can undergo anaerobic fermentation by colonic bacteria.

Clinically, one can take advantage of the rate of appearance of

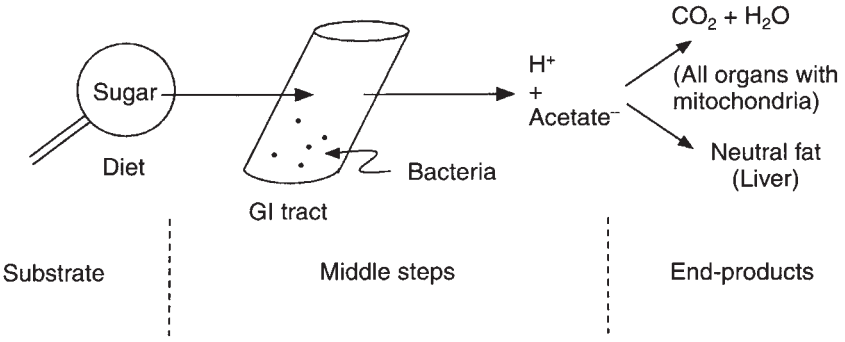

Fig. 4. *Metabolic processes and H^+ ion balance.* In this metabolic process, the starting point is dietary sugar and the end point is either exhaled CO_2 or storage fat. This has no acid-base consequences. Should either more acetic acid be produced or if the metabolism of acetic acid by the host be slowed down, acetic acid could accumulate and cause metabolic acidosis.

organic acids to deduce whether bacteria are still metabolically active in the small intestine. For example, once the metabolic acidosis due to over-production of organic acids is well controlled, the patient could be given a "diagnostic challenge," the consumption of a small quantity of sugar. If organic acids accumulate in plasma or urine, or if there is a fall in the plasma [HCO_3^-] because organic acids accumulated within the GI tract, one can infer that bacterial overgrowth may still be a potential hazard; a more specific, prolonged, and/or aggressive therapy is needed.

(b) Bacterial populations. Not all bacteria produce organic acids in general, or the specific ones such as D- versus L-lactic acid at equivalent rates. For example, the lactobacillae are much more likely to generate lactic acid than other species such as clostridia in the normal colonic flora. A decrease in luminal pH favors the growth of the acid tolerant bacterial species such as lactobacillus and the disappearance of the predominant, less acid tolerant gut flora [5]. Lactobacilli possess the enzyme DL-lactate racemase, and hence D-lactate may be formed from pyruvate via D-lactate dehydrogenase or from L-lactate by racemization [42]. Thus measures such as the use of antibiotics which change the proportions and amounts of bacteria in the GI tract may lead to an altered rate of production of D-lactic acids [5].

(c) Local pH. Two main factors have been proposed to cause bacterial overgrowth in the small intestine. First, certain bacteria (such as lactobacilli) increase in number in direct proportion to the presence of a more acid luminal fluid pH. Second, organic acid production may be influenced by the luminal fluid pH [43]. In more detail, when one of the products (H^+) of anaerobic glycolysis accumulates, the rate of glycolysis declines [44]; a proposed mechanism is that H^+ inhibits a key regulatory enzyme, phosphofructokinase-1 [45]. If the same type of controls were to operate in the bacterial species that happened to populate the area of the GI tract that received carbohydrates in the luminal fluid, one could speculate that more lactic acid might be formed if the fluid bathing these bacteria had a larger buffer capacity. Hence if more bicarbonate-rich fluid were delivered to the site where fermentation occurs due, for example, to the ingestion of alkali or the use of blockers of gastric HCl secretion such as H_2-antagonists or inhibitors of the gastric H^+/K^+ ATPase, one might find a larger production of organic acids by this fermentation route. Although one might reach a similar "limiting" low luminal pH, the quantity of organic acids produced could differ markedly depending on the buffer capacity of the fluid delivered there. It is important to recall that the [H^+] at a pH of 5 is only 0.01 mmol/liter, representing an exceedingly small quantity of organic acids in the absence of suitable H^+ acceptors.

Acid-base aspects of organic acid production in the GI tract

The primary basis of the metabolic acidosis due to organic acids such as D-lactic acidosis is an accelerated rate of production. Nevertheless, metabolism of organic acids occurs primarily in the liver, but also in organs such as the kidney. Hence with liver and renal failure, the degree of organic acid accumulation could be much greater for a given rate of production in the GI tract. To analyze the acid-base consequences from a quantitative perspective, several biochemical and metabolic considerations must be appreciated. Our approach to this problem will be as follows: first, we use a "metabolic process" analysis because this permits us to focus only on substrates and products, ignoring all metabolic intermediates and cofactors. In this way, we can simplify all metabolic pathways into three overall processes: (1) the conversion of dietary fuels to energy storage compounds (glycogen, triglycerides), (2) the conversion of dietary, or (3) the conversion of storage fuels to yield ATP as needed [46]. Only the latter two processes, if interrupted, have acid-base consequences. Another important metabolic aspect of regulation of organic acid removal is the ability of the patient to oxidize these fuels. Here, two points will be stressed. There is a limit on the capacity to oxidize fuels, a limit set by the rate of turnover of ATP. Even within this latter constraint, the competition between fuels as the precursor to be oxidized to yield the needed ATP sets another limit of the rate of oxidation of a specific fuel.

Metabolic process analysis

To define whether H^+ are produced or removed during metabolism, one need only count the valence of all substrates and products involved in that process [46]. The sum of the valence of cofactors can be ignored as these cofactors are both formed and removed and they are present in only catalytic amounts. When the net valence of products is more anionic or less cationic than substrates, H^+ have accumulated; the converse is also true. Further, one need not be concerned with which organ performs the metabolism because metabolic processes typically span more than one organ (Fig. 4).

One can define the metabolic process involving D-lactic acid as follows: the key steps are first, the mixing of neutral sugars and bacteria; second, anaerobic fermentation of sugars by bacteria yielding D-lactate anions plus H^+; third, the possible absorption of these organic acids from the GI tract; fourth, retention of the H^+ and anions in the body; fifth, if these anions are converted to neutral end-products in the body (glucose, glycogen, triglycerides

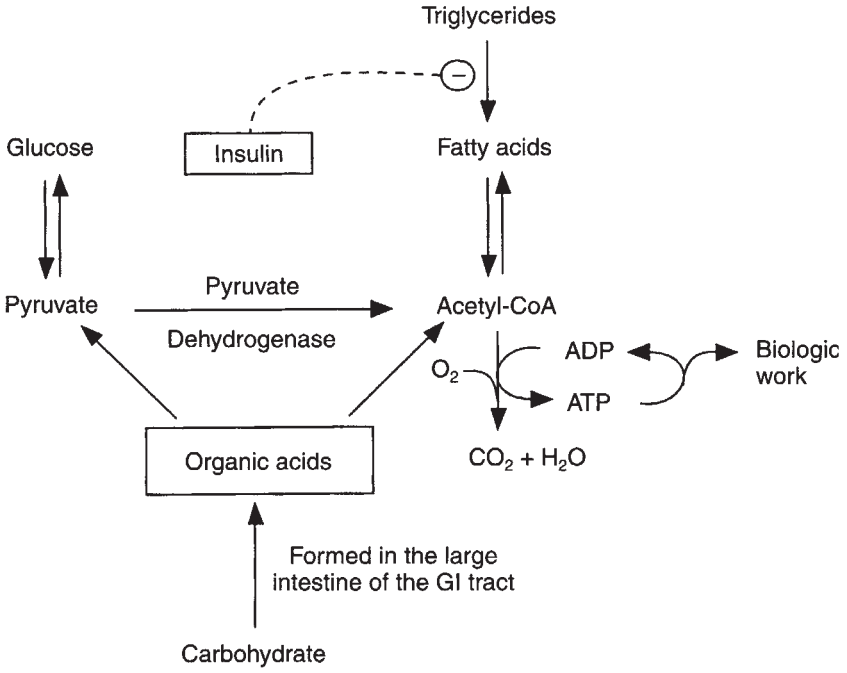

Fig. 5. *Acceleration of the oxidation of D-lactate by insulin.* Insulin may lead to an increase in the rate of oxidation of D-lactate by decreasing the supply of fatty acids, the alternate fuel.

or CO_2 plus H_2O) or if the anions are excreted in the urine with NH_4^+ or H^+, acidosis is avoided.

Removal of organic acids by host metabolism, quantitative and metabolic considerations

Pertinent principles of metabolic regulation. Three important aspects of metabolic regulation that are central to this discussion will be examined. First, fuels can only be metabolized in organs which possess the enzymes to initiate their metabolism. This in fact means the liver for many fuels [46]. Second, the rate of conversion of ATP to ADP (performance of biologic work) sets the upper limit on the rate of oxidative metabolism [17, 47]. Third, there is a competition between fuels for oxidation, largely controlled by the activity of the enzyme pyruvate dehydrogenase (PDH) (Fig. 2) [18]; PDH is inhibited when fatty acids are oxidized [48, 49].

The organic acids that are absorbed from the GI tract are delivered to the liver via the portal blood. From the point of view of hepatic metabolism, one can divide these organic acids into two classes depending on whether their immediate metabolism yields the substrate (pyruvate) or the product (acetyl-CoA) of PDH (Fig. 2). In simplest terms, those organic anions which cannot be converted to pyruvate (butyrate, acetate) have only three possible major metabolic fates: (1) oxidation yielding ATP, CO_2 and water; (2) with the appropriate hormonal milieu (high insulin and low glucagon levels in the fed state [50, 51], they may become substrates for the synthesis of long-chain fatty acids; (3) if lipogenesis is inhibited, the acetyl-CoA may be converted to ketoacids if hepatic need for ATP regeneration has already been largely accomplished by the oxidation of some of these organic acids or long-chain fatty acids of endogenous origin [17, 52, 53]. In contrast, organic anions such as D-lactate and propionate can be converted to pyruvate which, in turn, can be made into glucose or glycogen in the liver or kidney cortex (Fig. 2). Hence the options for removal of these organic acids by metabolic means are greater.

Table 1. Quantitative considerations for the oxidation of organic acids

Organic acid	Number H^+/mole	ATP yield upon complete oxidation
Acetic acid	1	10
Butyric acid	1	25
Propionic acid	1	18
D-lactic acid	1	17

Enzymes to initiate the metabolism of D-lactic acid. Although humans lack D-lactate dehydrogenase, they do metabolize D-lactate [54–57]. The specific enzyme to initiate the metabolism of D-lactate is D-α-hydroxy acid dehydrogenase [58–60], a flavoprotein enzyme with high activity in the liver and kidney cortex. Oh et al [54] estimated that at a serum concentration of 5 to 6 mEq/liter, a 70 kg man would be able to metabolize about 2500 mmoles of D-lactate per day. Nevertheless, the overall rate of oxidation of L-lactate is considerably faster than its D-isomer [54, 55]. Estimates from total body clearance rates suggest that the L-isomer is metabolized at a rate that is close to fivefold greater than D-lactate. A note of caution is important here. These data only apply to the clinical settings under which these experiments were carried out. Different rates would likely apply depending on the hormonal milieu (activity of PDH) and the overall rate of ATP turnover.

Availability of ADP. The rate of oxidation of organic anions and thereby the ability to remove H^+ ions by metabolism may be influenced by the rate of metabolic work (the rate of generation of ADP to permit oxidative metabolism [17, 19]). To the extent that a patient is hypothermic, has low motor activity, or received drugs that slow the metabolic rate such as sedatives or anaesthetics, the

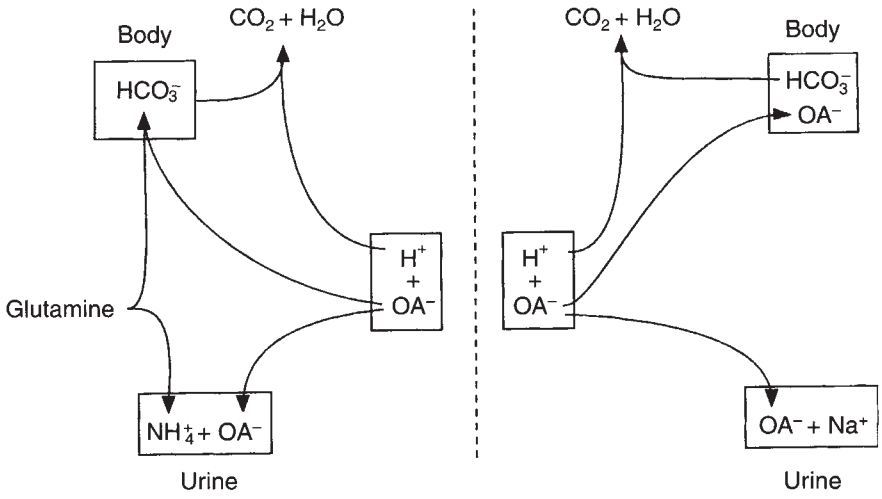

Fig. 6. *Organic acids and metabolic acidosis.* Organic acids have been produced as illustrated in the center of the diagram. All fates to the left of the dashed line have no acid-base consequences because bicarbonate is produced when the organic anion is metabolized to a neutral end-product (top left) or is excreted with H^+ or NH_4^+ ions (bottom left). In contrast, acidosis is produced with fates to the right of the dashed line, when the organic anions are retained in the body (top right) or excreted as their Na^+ and/or K^+ salts (bottom right).

rate of oxidation of all fuels, including organic acids, will be slower. This in turn, could lead to a greater degree of metabolic acidosis when the rate of organic acid production is high.

Control by fuel selection. The availability of fuels competing for oxidation may slow the rate of oxidation of D-lactic acid. For example, when insulin is deficient, a greater availability of fatty acids may lead to a lower rate of oxidation of D-lactic acid given the relatively fixed rate of ATP turnover. Hence we speculate that the administration of insulin, which should diminish the availability of fatty acids, might lead to a greater rate of oxidation of organic acids produced in the GI tract (Fig. 5); there are no data to test this hypothesis. Therefore, in a special case where metabolic acidosis with an elevated anion gap is *very* severe and *increasing* in degree, this option for therapy could be considered. Steps must also be taken to avoid hypoglycemia and a severe degree of hypokalemia. It would be interesting to evaluate this potential therapeutic approach in future clinical studies.

There is yet another way the degree of organic acidosis may be influenced by fuel selection, that is, the competition of these organic acids for oxidation. For example, if acetyl-CoA, the product of acetic acid and butyric acid oxidation accumulates, it will lead to inhibition of PDH (Fig. 2) [48, 49, 61, 62]. Therefore, with the combined production of acetic and D-lactic acids, only D-lactic acid may accumulate if oxidation is the primary metabolic fate of these acids. Moreover, the stoichiometry between proton removal and ATP regeneration is not identical for these organic acids of GI origin (Table 1). For example, the complete oxidation of 1 mmol of acetic acid will regenerate 10 mmol ATP [63]. In contrast, the complete oxidation of 1 mmol of butyric, D-lactic, or propionic acid will regenerate close to twice this quantity of ATP. Since each of these organic anions has a valence of one, they are all associated with the same H^+ load on a molar basis. Hence for a given rate of turnover of ATP, the accumulation of H^+ would be twice as high with the latter three organic acids than with the same molar load of acetic acid if oxidation was their only metabolic fate.

Clinical presentation, the plasma anion gap

There are two major ways acidosis is defined from routine laboratory data. First, organic acids may be added to the body so quickly that both the H^+ and the anion are retained; this results in metabolic acidosis and an elevated value for the plasma anion gap [64–66] (upper right portion of Fig. 6). Second, metabolic acidosis may be present without a rise in the plasma anion gap. In this latter setting, either the D-lactate anion was retained in the lumen of the GI tract (with the H^+ being absorbed or titrated by bicarbonate in the lumen of the GI tract), or it was excreted in the urine, but in either case, the cation lost with it was Na^+ and/or K^+ ion [67] (not a H^+ or NH_4^+ ion, lower right portion of Fig. 6). This latter type of metabolic acidosis is akin to the over-production of hippuric acid in glue sniffers [68]. Since D-lactate anions are reabsorbed by the kidney much less readily than is L-lactate [54, 69, 70], as time progresses, the anion gap may decline without resulting in a rise in the plasma bicarbonate concentration-that is, D-lactate is excreted as its Na^+ or K^+ salt (Fig. 6). Hence there are a number of mechanisms that may contribute to the presentation whereby the rise in the plasma anion gap might not match the fall in the plasma bicarbonate concentration. Not only might this lead to a diagnostic problem, it has implications for therapy because, once the organic anions are excreted as their Na^+ or K^+ salts, these anions are no longer available for metabolism to regenerate bicarbonate, and the patient might have developed a deficit of Na^+ and/or K^+.

Renal aspects: Excretion of organic anions with or without NH_4^+

Metabolic acidosis will occur if the organic anions are excreted in the urine with a cation other than H^+ or NH_4^+. Very few of these organic anions are excreted in appreciable amounts with H^+ ions because their pKs are not greater than 5. One might anticipate that the rate of excretion of NH_4^+ might be lower than expected for a number of reasons in patients with a high rate of production of organic acids in the GI tract. Coexistence of renal damage may be due directly to the GI lesion, drugs used to treat that GI problem, or even indirectly via chronic hypokalemia [71, 72]. In addition, several other factors might operate to lower the rate of excretion of NH_4^+. First, if the over-production of acids is acute, a high rate of excretion of NH_4^+ is not expected because there is normally a lag period of days before NH_4^+ production is augmented [73]. Second, if the patient is malnourished, the level of glutamine in plasma may be low enough to limit renal NH_4^+ production [74]. Third, since the production of NH_4^+ also results in the regeneration of ATP in cells of the proximal tubule [75], two additional mechanisms might lead to a lower rate of NH_4^+

excretion: (1) a lower filtered load of Na^+ due to a low GFR because of ECF volume contraction lessens the need for consumption of ATP (Na^+ reabsorption) in the proximal tubule. (2) If the organic acids are oxidized in proximal tubular cells to yield ATP, less glutamine can now be metabolized in these cells, and hence the rate of ammoniagenesis could decline for this reason as well [73].

Concluding remarks

There are a variety of clinical presentations when organic acids are over-produced in the GI tract. In its most benign form, there is no systemic acid-base disorder, but local colonic irritation with crampy pain and diarrhea are the main complaints, as in lactose intolerance. The most common clinical acid-base disturbance related to organic acid production in the GI tract is metabolic acidosis with an increased anion gap in plasma. A third type of presentation is metabolic acidosis with a lower than expected rise or even a near normal anion gap in plasma. Its pathophysiology could include two different explanations. First, there may be the renal excretion of organic anions such as D-lactate without H^+ or NH_4^+ ions and reflects the fact that the D-isomer is less well reabsorbed in the proximal convoluted tubule than the normal L-isomer of lactic acid. Second, some patients with a short bowel may lose the Na salt of D-lactic acid in the stool, which also causes metabolic acidosis without a rise in the plasma anion gap [the H^+, but not the organic anion is reabsorbed (or reacts with secreted bicarbonate in the lumen of the GI tract)]. The metabolic considerations that might limit the rate of removal of H^+ by metabolism of anions or the urinary excretion of NH_4^+ in these patients were addressed. While limiting the supply of dietary sugars to intestinal bacteria may lessen the degree of acidosis, organic acids may be removed more rapidly by oxidation if the availability of the competing fuels such as fatty acids is decreased. The oral administration of poorly absorbable antibiotics (such as vancomycin, neomycin) was shown to be beneficial in eliminating the pathological bacteria in some of these patients [3, 5, 11]. Surgical intervention which increases the length of intestinal surface for absorption of sugar or re-establishing intestinal continuity may be necessary in some patients with D-lactic acidosis associated with intestinal bypass [42].

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